

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450, ON THE DATE INDICATED BELOW.

BY: Ira Horn Date: October 26, 2004

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Patent of:  
TOMOHIRO YAMAMOTO ET AL.

Patent No.: US 6,776,888 B2

Appln. No.: 10/089,289

Title: BIOSENSOR

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:  
:  
Issue Date: August 17, 2004  
:  
Filing Date: March 26, 2002  
:  
Attorney Docket No.: 10059-411US  
:  
(P26049-01)

Certificate  
NOV 03 2004  
of Correction

**REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR § 1.322**

Enclosed herewith are the original and one copy of a Certificate of Correction Form PTO 1050, correcting errors which appeared in the printing of the above-identified patent.

The errors appears on the face of the patent and in claim 5. On the face of the patent in the PCT Pub. Date section, the date should read Feb. 7, 2002 and on claim 5, line 39, the claim should read "The biosensor of claim 1,". It is submitted that the U.S. Patent and Trademark Office is responsible for the error. Enclosed is a copy of the PCT Pub. WO02/010735 and a copy of claim 5. Accordingly, no fee should be due.

However, the Commissioner is hereby authorized to charge and/or credit **Deposit Account No. 50-1017 (Billing No. 210059.0411)** for any fee due. A duplicate copy of this sheet is enclosed.

Issuance of a Certificate of Correction is believed appropriate and is respectfully solicited..

Respectfully submitted,

October 25, 2004  
(Date)

By: TOMOHIRO YAMAMOTO ET AL.

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WWS:TMF  
Enclosure

NOV 08 2004

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UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

REGISTRATION NO. : US 6,776,888 B2

DATED : August 17, 2004

INVENTOR(S) : Tomohiro Yamamoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

On the face of the patent the PCT Pub. Date in item (87) should read as follows:

-- PCT Pub. Date: Feb. 7, 2002 --

In the Claims Section of the patent, claim 5, line 39 of column 12, should read as follows:

"bio sensor" should read -- biosensor--

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PATENT NO. US 6,776,888 B2

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(12) **United States Patent**  
Yamamoto et al.

(10) Patent No.: **US 6,776,888 B2**

(45) Date of Patent: **Aug. 17, 2004**

(54) **BIOSENSOR**

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(21) Appl. No.: 10/089,289

(22) PCT Filed: Jul. 26, 2001

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(2), (4) Date: Mar. 26, 2002

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(58) Field of Search ..... 204/403.01, 403.05,  
204/403.06, 403.09, 403.1, 403.14

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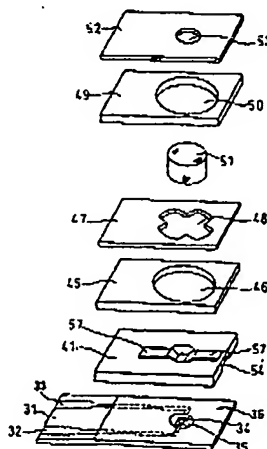
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(57) **ABSTRACT**

The present invention provides a biosensor that enables highly-accurate measurement of a sample solution including a solid component like hemocytes and has a little variation in response. The biosensor includes: an insulating base plate, an electrode system having at least a working electrode and a counter electrode provided on the base plate, a cover member that is combined with the base plate to define a sample solution supply pathway for leading a sample solution from a sample supply unit to the electrode system, a reaction reagent system including at least an oxidation-reduction enzyme and an electron mediator, and a filter disposed between the electrode system and the sample supply unit in the sample solution supply pathway. The biosensor has a space that encircles surface of the filter in an area from one end of the filter close to the sample supply unit to the other end of the filter close to the electrode system. This arrangement effectively prevents the solid component like hemocytes from flowing into the electrode system without being filtered out by the filter.

**17 Claims, 9 Drawing Sheets**



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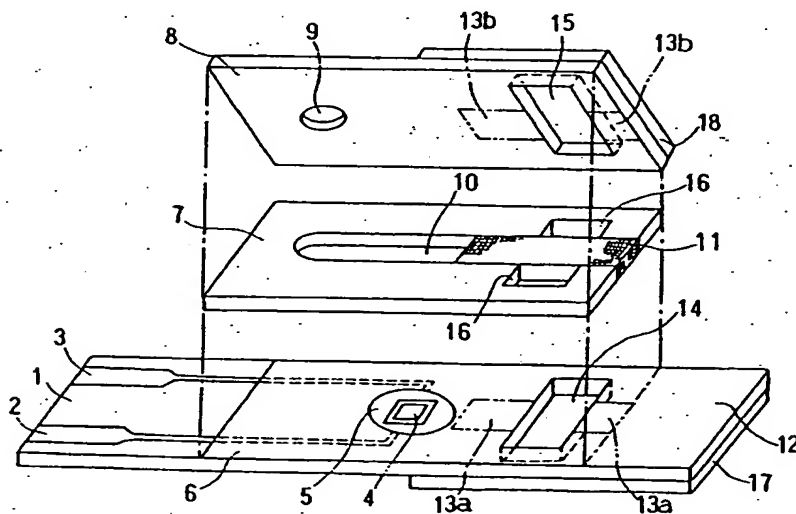
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[続葉有]

(54) Title: BIOSENSOR

(54) 発明の名称: バイオセンサ



(57) Abstract: A biosensor capable of accurately measuring even a specimen liquid containing a solid composition such as blood corpuscle and providing less variation in response value, comprising an insulating substrate, an electrode system at least having an acting electrode and an electrode opposite to the acting electrode installed on the substrate, a cover member combined with the substrate to form a specimen liquid feed path for leading a specimen liquid from a specimen feed part to the electrode system in the space thereof from the substrate, a reaction reagent system containing at least oxidoreductase and electronic mediator, and a filter disposed between the electrode system and the specimen feed part in the specimen feed path, wherein a space part surrounding all side end thereof, whereby the solid composition such as blood corpuscle is prevented from flowing into the electrode system without being filtrated through the filter.

[続葉有]

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## US 6,776,888 B2

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method at the specified position covering over the electrode system on the base plate. In this example, as shown in FIG. 4, the reaction reagent system was composed of a porous carrier 24, which was in contact with an end of the filter 11 and had enzymes, a surface active agent, and an electron mediator soaked therein and carried thereon, and the CMC layer 21 formed by the air drying method at the specified position covering over the electrode system on the base plate.

The arrangement of making part of the reagents included in the reaction reagent system carried on the porous carrier enhances the solubility of the reaction reagents into the sample solution, as in the case of the freeze drying method.

Like Example 1, the process first added a 0.5% by weight of aqueous solution of CMC as the hydrophilic polymer dropwise onto the electrode system and dried the solution in a hot blast drier at 50° C. for 10 minutes, so as to form the CMC layer 21.

The process bonded and fixed the porous carrier 24 made of felt which was cut into the size of 2x4.5 mm and mainly composed of glass filters at a specified position shown in FIG. 4 on the cover in the sample solution supply pathway with a cellulose-based adhesive (Cemedine C manufactured by Cemedine Co., Ltd), so as to be in contact with an end of the filter 11.

The process added 5 µl of the aqueous solution, in which cholesterol oxidase, cholesterol esterase, potassium ferricyanide, and Triton X-100 were dissolved as in the case of Example 1, dropwise onto the porous carrier 24, made the solution homogeneously soak into the porous carrier 24, and dried the solution in a hot blast drier at 50° C. for 15 minutes.

Like Example 1, the process located the filter and joined the cover member with the base plate 1 to complete a biosensor. The porous carrier 24 had the thickness of approximately 0.1 to 0.2 mm. The distance between the base plate 1 and the cover 8 in the part of the sample solution supply pathway closer to the electrode system was accordingly set equal to 0.3 mm, which was significantly greater than 0.1 mm in the structure of Example 1. In Example 2, GB100R was applied for the filter 11.

This biosensor showed a response corresponding to the concentration of cholesterol at three minutes after the dropwise addition of the whole blood sample to the sample supply unit.

In the above examples, the base plate 1 and the cover 8 were made of a transparent material, so that the flow-in state of the sample was observable with naked eyes.

In the above examples, the specific part of the slit 10 for forming the sample solution supply pathway with the filter fitted therein has a width equal to the width of the part that has the electrode system and receives a flow of the sample passing through the filter. One of these parts may be narrower than the other. FIG. 5 shows the positional relationship between the spacer and the filter and their shapes in such an example.

The arrangement of the reagents constituting the reaction reagent layer and their carrying method are not restricted to the specifications of the above examples, as long as the reagents in the reaction reagent system are quickly dissolved in the sample solution to ensure smooth progress of the enzyme reaction.

## INDUSTRIAL APPLICABILITY

As described above, the present invention effectively prevents a solid component like hemocytes included in a

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sample solution from coming into contact with the electrode system and the reaction reagent system and thereby provide a biosensor that ensures highly accurate measurement and has a little variation in response.

What is claimed is:

1. A biosensor comprising:

an insulating base plate,

an electrode system that is provided on the base plate and has at least a working electrode and a counter electrode, a cover member that is combined with the base plate to define a sample solution supply pathway for leading a sample solution from a sample supply unit to the electrode system, wherein the sample supply unit is located on a side of the electrode system,

a reaction reagent system including at least an oxidation-reduction enzyme and an electron mediator, and

a filter in the sample solution supply pathway, the filter disposed between the electrode system and the sample supply unit,

the biosensor having a space that encircles the surface of the filter in an area located between a first end of the filter close to the sample supply unit and a second end of the filter close to the electrode system, wherein said space has a width of 0.5 mm to 5.0 mm.

2. The biosensor of claim 1, wherein the cover member is disposed above the base plate, and the sample solution supply pathway starts from the sample supply unit provided on the base plate and is formed along the cover member and the base plate.

3. The biosensor of claim 1, wherein the space has a width of 1.0 mm to 3.0 mm.

4. The biosensor of claim 1, wherein the filter is a porous body having spaces connecting with one another in a three-dimensional manner, and the porous body moves blood from the sample supply unit toward the sample solution supply pathway by capillarity and functions to filter hemocytes based on a difference between the flow resistance of plasma and the flow resistance of hemocytes.

5. The biosensor of claim 1, wherein the oxidation-reduction enzyme is cholesterol oxidase.

6. The biosensor of claim 1, wherein the reaction reagent system includes an enzyme having an ability of hydrolyzing cholesterol ester.

7. The biosensor of claim 6, wherein the enzyme having the ability of hydrolyzing cholesterol ester is cholesterol esterase.

8. The biosensor of claim 1, wherein the reaction reagent system includes a surface active agent.

9. The biosensor of claim 1, wherein part or all of the cover member and of the insulating base plate are transparent.

10. A biosensor comprising:

an insulating base plate,

an electrode system that is provided on the base plate and has at least a working electrode and a counter electrode,

a cover member that is combined with the base plate to define a sample solution supply pathway for leading a sample solution from a sample supply unit to the electrode system, wherein the sample solution supply pathway is disposed in a direction of gravity from the sample supply unit provided on the cover member,

a reaction reagent system including at least an oxidation-reduction enzyme and an electron mediator, and

a filter in the sample solution supply pathway, the filter disposed between the electrode system and the sample supply unit,

**Amendment to and Listing of the Claims:**

1. to 14. (Canceled)

15. (New) A biosensor comprising:

an insulating base plate,

an electrode system that is provided on the base plate and has at least a working electrode and a counter electrode,

a cover member that is combined with the base plate to define a sample solution supply pathway for leading a sample solution from a sample supply unit to the electrode system, wherein the sample supply unit is located on a side of the electrode system,

a reaction reagent system including at least an oxidation-reduction enzyme and an electron mediator, and

a filter in the sample solution supply pathway, the filter disposed between the electrode system and the sample supply unit,

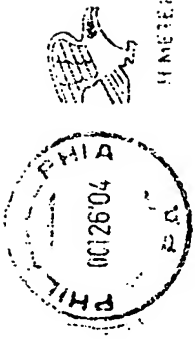
the biosensor having a space that encircles the surface of the filter in an area located between a first end of the filter close to the sample supply unit and a second end of the filter close to the electrode system, wherein said space has a width of 0.5 mm to 5.0 mm.

16. (New) The biosensor of claim 15, wherein the cover member is disposed above the base plate, and the sample solution supply pathway starts from the sample supply unit provided on the base plate and is formed along the cover member and the base plate.

17. (New) The biosensor of claim 15, wherein the space has a width of 1.0 mm to 3.0 mm.

18. (New) The biosensor of claim 15, wherein the filter is a porous body having spaces connecting with one another in a three-dimensional manner, and the porous body moves blood from the sample supply unit toward the sample solution supply pathway by capillarity and functions to filter hemocytes based on a difference between the flow resistance of plasma and the flow resistance of hemocytes.

*claim 5*  
[X 19. (New) The biosensor of claim 15, wherein the oxidation-reduction enzyme is cholesterol oxidase.]



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